DEPARTMENT OF THE AIR FORCE
59TH MEDICAL WING (AETC)
JOINT BASE SAN ANTONIO - LACKLAND TEXAS

21 FEB 2017

MEMORANDUM FOR SGOZ
ATTN: MAJ BRYANT J. WEBBER

FROM: 59 MDW/SGVU

SUBJECT: Professional Presentation Approval

1. Your paper, entitled **Challenges with Diagnosing and Investigating Potential Active Tuberculosis Disease in Military Trainees** presented at/published to **Medical Surveillance Monthly Report (MSMR)** in accordance with MDWI 41-108, has been approved and assigned local file #**17102.**

2. Pertinent biographic information (name of author(s), title, etc.) has been entered into our computer file. Please advise us (by phone or mail) that your presentation was given. At that time, we will need the date (month, day and year) along with the location of your presentation. It is important to update this information so that we can provide quality support for you, your department, and the Medical Center commander. This information is used to document the scholarly activities of our professional staff and students, which is an essential component of Wilford Hall Ambulatory Surgical Center (WHASC) internship and residency programs.

3. Please know that if you are a Graduate Health Sciences Education student and your department has told you they cannot fund your publication, the 59th Clinical Research Division may pay for your basic journal publishing charges (to include costs for tables and black and white photos). We cannot pay for reprints. If you are 59 MDW staff member, we can forward your request for funds to the designated wing POC.

4. Congratulations, and thank you for your efforts and time. Your contributions are vital to the medical mission. We look forward to assisting you in your future publication/presentation efforts.

Linda Steel-Goodwin

LINDA STEEL-GOODWIN, Col, USAF, BSC
Director, Clinical Investigations & Research Support

PROCESSING OF PROFESSIONAL MEDICAL RESEARCH/TECHNICAL PUBLICATIONS/PRESENTATIONS

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USE ONLY THE MOST CURRENT 59 MDW FORM 3039 LOCATED ON AF E-PUBLISHING

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1. TO: CLINICAL RESEARCH	2. FROM: (Author's Name, Rank, Grade, Office Symbol)	3. GME/GHSE STUDENT:	4. PROTOCOL NUMBER:
	Bryant J. Webber, Maj, O-4, 559 THLS/SGOZ	☐ YES ☒ NO	20170045N

5. PROTOCOL TITLE: (**NOTE:** For each new release of medical research or technical information as a publication/presentation, a new 59 MDW Form 3039 must be submitted for review and approval.)

Challenges with Diagnosis and Contact Investigation of Active Tuberculosis in Military Trainees

6. TITLE OF MATERIAL TO BE PUBLISHED OR PRESENTED:

Challenges with Diagnosing and Investigating Potential Active Tuberculosis Disease in Military Trainees

7. FUNDING RECEIVED FOR THIS STUDY? ☐ YES ☒ NO FUNDING SOURCE:

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Medical Surveillance Monthly Report (MSMR)

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16. AUTHORSHIP AND CO-AUTHOR(S) List in the order they will appear in the manuscript.

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17. IS A 502 ISG/JAC ETHICS REVIEW REQUIRED (JER DOD 5500.07-R)? ☐ YES ☒ NO

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Challenges with Diagnosing and Investigating Potential Active Tuberculosis Disease in Military Trainees

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Abstract

Fourteen U.S. and international military personnel training at Joint Base San Antonio-Lackland, Texas, were hospitalized due to potential pulmonary tuberculosis (TB) between January 2010 and December 2016, of whom 5 were diagnosed with active disease. The incidence rate in the training population was 1.89 per 100,000 (95% confidence interval: 0.81, 4.42), with a higher rate when restricting to international military students attending the Defense Language Institute English Language Center. Given a variety of atypical presentations and the diagnostic and public health challenges they created, we performed a retrospective review of all hospitalized cases (with the exception of one published previously). This case series highlights the importance of a high index of clinical suspicion when TB is being considered in closely congregated settings, and the risk of overreliance on acid fast bacilli staining and nucleic acid amplification testing for ruling out active pulmonary disease in young, otherwise healthy trainees. Practical solutions are suggested.

Introduction

The incidence of active tuberculosis (TB) disease in the general U.S. population[1] and the U.S. military[2] has declined over the past two decades, with foreign birth remaining one of the strongest correlates of risk. This disparity between foreign- and U.S.-born persons, and its implications for prevention and elimination, is particularly important at Joint Base San Antonio (JBSA)-Lackland. One of the largest military installations in the United States, JBSA-Lackland hosts three training platforms that include a high volume of foreign-born students: the Defense Language Institute English Language Center (DLIELC), which conducts English language training for international military and civilian personnel from over 110 countries; the Inter-American Air Forces Academy (IAAFA), which provides military and technical education to air force members representing over 20 Latin American and Caribbean countries; and Basic Military Training (BMT), the initial entry training for all enlisted members of the U.S. Air Force, among whom 1-2% were born overseas.

Current TB screening programs vary by training platform. International military students are required to have a screening chest x-ray as part of their medical packet prior to arrival. Projected aviators are also screened with a chest x-ray during their flight physical, conducted at variable times during training. New U.S. Air Force recruits are universally screened during BMT in-processing week. Those born in the United States and who report no history of a positive tuberculin skin test (TST) are screened with a single TST; all others are screened with an interferon gamma release assay (IGRA)—previously the QuantiFERON-TB or QuantiFERON-TB Gold, and currently, as of January 2017, the T-SPOT TB.

Regardless of birthplace, persons with pulmonary TB may present with a variety of clinical features. Atypical presentations can pose diagnostic challenges, resulting in potentially serious treatment delays,[3,4] delayed contact investigations, and increased transmission risk. Due to close quarter living arrangements[5] and a degree of stress-induced immunosuppression,[6] this risk may be greater in military training environments. We have recently encountered several atypical presentations of active TB, as well as potential cases that were eventually diagnosed otherwise, among our population of trainees at JBSA-

Lackland. We initiated this retrospective case series to review the challenges and lessons learned from these atypical presentations.

Methods

All trainees at JBSA-Lackland who potentially have active TB disease, whether identified through screening or clinical symptoms, are admitted to the San Antonio Military Medical Center (SAMMC) for evaluation. Using the trainee health hospitalization registry and cross-referencing against consult records of the SAMMC Infectious Disease Service, we generated a case list of all JBSA-Lackland trainees hospitalized for TB rule-out between 1 January 2010 and 31 December 2016.

For each case we conducted a chart review to collect the following information: age, sex, country of birth, and state of birth, if U.S.-born; history of Bacillus Calmette–Guérin (BCG) vaccination; type and duration of symptoms, if any; results of TST, IGRA, chest x-ray, and chest computed tomography (CT); acid fast bacilli (AFB) staining, culture, and GeneXpert, an automated nucleic acid amplification test used to detect *M. tuberculosis* DNA; and final diagnosis. For those with culture-positive TB, we also obtained drug resistance testing for first line anti-TB drugs, either through the electronic health record or regional health department. For foreign-born trainees without any BCG documentation in the record, we presumed vaccination based on country-specific standard policy, as outlined in the BCG World Atlas (http://www.bcgatlas.org/). We also reviewed the public health contact investigations performed for the cases of confirmed pulmonary TB.

To understand the burden of disease in the population, we calculated the incidence rate of active TB with 95% confidence intervals (CI), both collectively and stratified by training platform.

Results

A total of 14 trainees were hospitalized for TB evaluation during the 7-year study period. One case of active pulmonary TB in a DLIELC student was previously published[7] and thus excluded. Of the remaining 13 trainees, denoted A-M, all were male and young, with an age range of 19 to 29 years. Half (4/8) of the BMT trainees and all (5/5) of the DLIELC trainees were born overseas. A slight majority (7/13) were asymptomatic at the time of hospital admission, and TST and IGRA results were highly

variable (**Table 1a**). All trainees had abnormalities on their chest x-ray, chest CT, or both with predominantly upper lobe involvement and a minority demonstrating cavitation (**Table 1b**).

Four of the trainees were diagnosed with active TB disease: trainees A and C with culture-positive pulmonary TB; trainee B with culture-negative pulmonary TB; and trainee D with culture-positive pulmonary TB and concurrent genitourinary TB. The remaining 9 trainees received the alternative diagnoses of pneumonia (n=3), latent TB infection (n=2), prior treated pulmonary TB (n=1), non-TB mycobacterium (n=1), histoplasmosis (n=1), and nocardia (n=1) (**Table 1a**).

The 4 trainees with TB were evenly divided between DLIELC and BMT, and 3 were born overseas (Ghana, Saudi Arabia, and Cameroon). Presenting characteristics were atypical. Only trainee A reported respiratory symptoms, and these were most consistent with an afebrile upper respiratory infection. Trainees B and C were admitted due to high clinical suspicion of TB based on screening tests and imaging, while trainee D was hospitalized with scrotal pain potentially attributed to TB. Trainees A-C had repeated sputa, including induced sputa, that were AFB smear and GeneXpert negative, and diagnoses were made based on recovery of *M. tuberculosis* from culture, except for trainee B, who was diagnosed with culture-negative TB due to history and radiological features. Trainee D initially had three negative AFB smears and GeneXpert assays; after AFB smear and GeneXpert of a testicular abscess tested positive, a fourth sputum was obtained, which was smear and GeneXpert positive. All isolates from culture-positive cases were pan-susceptible to first line medications (**Table 2**).

During this period, the incidence rate of active TB in the JBSA training population (to include the previously published case) was 1.89 per 100,000 (95% CI: 0.81, 4.42). The rates were 13.1 (95% CI: 3.71, 35.7) and 0.83 (0.14, 2.73) in the DLIELC and BMT training platforms, respectively.

Editorial Comment

Among 13 trainees at JBSA-Lackland admitted for TB evaluation during the 7-year surveillance period, 4 were diagnosed with pulmonary TB disease. These cases were notable for their atypical presentations, all lacking the classic signs of prolonged fever, hemoptysis, anorexia, and unexplained weight loss, reaffirming that TB should not be ruled out on clinical features alone. The microbiologic

diagnosis was particularly challenging because AFB smear and GeneXpert results for all sputum samples were negative—except the fourth sample from trainee D, which was only obtained after the diagnosis of genitourinary TB was established. The diagnoses of pulmonary TB, and the ensuing contact investigations, were delayed until cultures returned as positive, up to 6 weeks after admission.[8] The lack of symptoms and low mycobacterial burden may have been due to host suppression in this cohort of otherwise healthy young males.[9]

This case series raises concern about the increasing reliance on molecular tests for rapid diagnosis of active TB. Although nucleic acid amplification tests have excellent overall accuracy for the detection of *M. tuberculosis* DNA from sputum samples,[10,11] their sensitivity decreases precipitously, to as low as 68%, when AFB smears are negative.[11] Bayesian approaches based on multiple rapid tests may not be ideal in situations when more definitive TB exclusion is desired, such as high volume military and educational settings.

Since these TB cases were largely AFB smear negative, and patients were mostly asymptomatic and had no cavitary lesions on plain radiographs, the risk for mycobacterial transmission was low.[12,13] In close congregate and mass training settings, however, even a low transmission risk poses outbreak potential. Because of this risk, using guidance from the Centers for Disease Control and Prevention, local public health officials gathered contact information on all 13 cases and conducted contact investigations for those eventually diagnosed as pulmonary TB. Investigations of the DLIELC cases proved challenging due to language barriers, politico-cultural sensitivities, and the transience and heterogeneity of the population. The heterogeneous trainee population was particularly problematic for establishing a baseline latent TB infection rate, which is required for concentric testing.[14,15] By extrapolating data from Saudi Arabian healthcare worker studies, a baseline rate of 10-15%[16,17] was established; given this baseline and the small denominator of exposed personnel, the investigation was expanded if the observed conversion rate exceeded 30%. In both the DLIELC and BMT cases, the duration between negative smears and positive cultures further complicated the investigations, as many potentially exposed persons had been moved to their next assignment or returned to their home country. Some individuals who had permanently

left the installation were unable to be contacted, highlighting the need to collect accurate, long-term personal contact information (e.g., cell phone and personal email).

In close congregate settings, it is crucial to maintain a high clinical suspicion and not prematurely dismiss cases of pulmonary TB. Clinicians should notify public health personnel as soon as pulmonary TB is being considered, rather than waiting to report once the diagnosis is officially established. Public health investigators and military training leadership have learned that it is essential to begin the preliminary stages of a contact investigation, and to establish a close working relationship with the clinicians overseeing the case, as soon as possible. This is especially prudent when the patient and exposed persons may be traveling internationally, which increases the resources necessary to conduct the investigation.

In light of these lessons learned, JBSA-Lackland has developed a new policy whereby BMT trainees hospitalized with suspected pulmonary TB, who are discharged without a diagnosis explaining their imaging (i.e., no TB or alternative diagnosis), may be placed on convalescent leave until at least 3 cultures are negative at the 6-week mark.[8] This recommendation is made on a case-by-case basis by a multi-disciplinary team, to include clinical and public health personnel, and presented to the training commander for a final decision. Since convalescent leave is not an option for students at the DLIELC, cases are discussed with training leadership and the country sponsor. If a student must be returned to training before active TB is formally ruled out, treatment for active TB can be considered, even in the absence of culture growth.[18]

Although active TB disease remains rare in the training population at JBSA-Lackland, a high degree of clinical suspicion should be maintained when trainees present with potential TB, particularly for those born overseas. Clinical suspicion should persist even if initial AFB smears and nucleic acid amplification testing are negative. Providers and public health personnel must communicate early and frequently to understand the nuances of the clinical workup and its implications for contact investigations.

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Table 1a. Description and Diagnoses of Trainees Hospitalized for Possible Active Tuberculosis, 2010-2016 (N=13)

	Year	*Age*	*Status*	*Birthplace*	*BCG*	*TST*	*IGRA*	*Symptoms*	*Diagnosis*
A	2012	21	BMT	U.S. (Texas)	No	29 mm	Positive	Cough, congestion x2 days	Pulmonary TB
B	2012	27	BMT	Ghana	Yes	N/A	Positive	None	Culture-negative TB
C	2015	19	DLI	Saudi Arabia	Yes	15 mm	Positive	None	Pulmonary TB
D	2016	23	DLI	Cameroon	Presumed†	"Reactive"	N/A	Testicular pain x5 months	Pulmonary and GU TB
E	2010	28	BMT	Peru	Presumed†	18 mm	N/A	Fever, chills, cough x2 weeks	Latent TB Infection
F	2010	19	BMT	U.S. (Arizona)	No	0 mm	Negative	Pleuritic chest pain x1 week	Nocardia
G	2010	20	BMT	Philippines	Yes	24 mm	Positive	None	Pneumonia
H	2012	22	DLI	Afghanistan	Presumed†	N/A	N/A	Cough x8 days; hemoptysis x1	Pneumonia
I	2015	29	DLI	Afghanistan	Presumed†	N/A	Positive	None	Latent TB Infection
J	2015	22	DLI	Saudi Arabia	Presumed†	0 mm	Indeterminate	Cough, congestion x8 days	Pneumonia
K	2016	21	BMT	U.S. (Ohio)	No	"Reactive"	Negative	None	Histoplasmosis
L	2016	19	BMT	Philippines	Yes	N/A	Positive	None	History of Treated TB
M	2016	19	BMT	U.S. (Texas)	No	27 mm	Positive	None	*Mycobacterium simiae*

Abbreviations: BCG, Bacillus Calmette–Guérin; BMT, Basic Military Training; DLI, Defense Language Institute; GU, genitourinary; IGRA, Interferon Gamma Release Assay; TB, Tuberculosis; TST, Tuberculin Skin Test

Table 1b. Imaging Results of Trainees Hospitalized for Possible Active Tuberculosis, 2010-2016 (N=13)

	Chest X-ray	*Chest Computed Tomography*
A	R apical opacities	R lung apex nodular opacities (largest 8 mm) with cluster GGO
B	RUL focal opacities	RUL focal opacification and coalescing lung nodules
C	RUL nodular opacities	RUL mass-like cavitary consolidation with TIB distribution, hilar lymphadenopathy
D	Unremarkable	R lung apex scarring, 13 mm juxtaesophageal lymph node with rim enhancement
E	RML cystic cavity (4.5 x 3.6 cm)	Unremarkable
F	LUL thin walled cavity (11 mm)	LUL cavity with surrounding consolidation (4.3 x 3.2 cm) with TIB distribution and GGO
G	Cardiac apex focal opacities	RLL, RML, and RUL apex patchy multifocal infiltrates
H	RUL focal consolidations	Not performed
I	RUL nodular opacities	RUL calcified nodularity with associated bronchiectasis
J	RUL and LLL consolidations	RUL and LLL consolidations with air bronchograms
K	LUL nonspecific lesion (2 cm)	LUL cavitary nodule (2 cm) with small adjacent airspace opacity
L	L apical nodular opacities	LUL and L apical calcified and non-calcified nodules with TIB distribution
M	Enlarged azygos shadow (1.3 cm)	RUL subplural nodular opacities (largest 16 mm) with TIB distribution and RLL GGO

Abbreviations: GGO, ground glass opacities; LLL, left lower lobe; LUL, left upper lode; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe; TIB, tree-in-bud

Table 2. Diagnostic Evaluation of Trainees Diagnosed with Active Tuberculosis

	AFB Source	*AFB Smear (Positive/Tested)*	*GeneXpert (Positive MTB/Tested)*	*AFB Culture (Positive MTB/Tested)*	*Drug Resistance*
A	Sputum	0/3	0/3	3/3	None (INH, RIF, EMB, PZA)
B	Sputum	0/6	0/1	0/6	
	Bronchoscopy	0/1	0/0	0/1	
C	Sputum	0/4	0/3	3/4	None (INH, RIF, EMB, PZA, STM)
D	First Sputum	0/3	0/3	2/3	
	Scrotum	1/1	1/1	1/1	
	Second Sputum	1/1	1/1	1/1	None (INH, RIF, EMB, PZA)

Abbreviations: AFB, Acid Fast Bacilli; EMB, ethambutol; INH, isoniazid; MTB, *Mycobacterium tuberculosis*; PZA, pyrazinamide; STM, streptomycin; RIF, rifampin